REMARKS

The above amendment cancels a claim which is clearly redundant. No new matter is added by this amendment. Each of the rejections will be set forth in more detail below under separate headings.

Rejection under 35 USC 112, second paragraph

Claim 22 was rejected as failing to further limit Claim 1, from which it depended. Claim 22 is canceled. Withdrawal of the rejection is requested,

The Claims

Claim 1 is illustrative and is directed to a method of delivering a therapeutic dose of a bioactive agent in a single breath activated step from a receptacle containing a mass consisting of particles wherein:

i) the particles administered to the subject's respiratory tract have a tap density of less than 0.4 g/cm^3;
ii) at least 50% of the particles have a fine particle fraction less than 4.0 μm; and
iii) at least about 50% of the mass of particles stored in the receptacle is delivered to the pulmonary system of the subject.

The invention relates to the discovery that a mass of particles can be efficiently and effectively delivered in large amounts in a single dose without the aid of carrier particles.

Rejection under 35 USC 102(e)

Claims 1-3, 8-9, 11-12, 15-22, 24 and 26-27 are rejected as being anticipated by Maa *et al.* (US Patent No. 6,284,282 B1).

Maa et al. is relied upon to teach methods of preparing a respirable dry protein powder and methods for delivering the protein powder. The preferred average size of the protein powder composition to be delivered is between 6 and 8 microns. (Col. 2, line 31.) The preferred tap density is less than 0.1 g/cm^3. (Col. 6, lines 8.) This composition may be substantially free of excipients. (Col. 2, line 32.) The fine particle fraction (FPF) is defined as the percentage of the

composition with "an aerodynamic mass median diameter of less than 6.8μm." (Col. 5, lines 60-62.) The compositions preferably have an FPF "of at least about 10%, with at least about 20% being preferred and at least about 30% being especially preferred, with some systems enabling very high FPFs, in the order of 40 to 50%." (Col. 5, line 66 et seq.) These compositions are preferably delivered by blending the composition with "bulking agents or carriers." Bulking agents are taught to "improve the dispersibility of the powder" (Col. 10, lines 39-47) and "are distinguishable from the use of bulking agents or carriers during the spray drying process." (Col. 10, lines 47-48.)

Turning to the exemplification of Maa et al., Example 1 compares spray drying and spray freeze drying protein compositions. When measuring the FPF, each powder was blended with a lactose carrier or bulking agent (Col. 17, lines 38-46), loaded into a dry powder inhaler (Col. 17, lines 47-49) and tested. The powder was added to the carrier in a ratio of 10:1 (carrier:powder). The total mass of product in the inhaler was between 10 and 20 mg. Thus, between 1 and 2 mg. of the protein composition was added to the inhaler. None of the examples of Maa *et al.* teach or disclose the FPFs of a composition free of bulking agent or carrier. Indeed, Maa *et al.* state at Col. 27, lines 44-45, that "powders with a high FPF (>40%) showed a homogeneous blending." This sentence suggests that the FPF (<6.8 microns) of powders that are not blended prior to loading the inhaler/receptacle possess FPF's (<6.8 microns) below 40%. Maa *et al.* do not teach an FPF, as defined by an aerodynamic mass diameter of less than 4 microns, for any product.

While the Examiner discusses what is taught by Maa *et al.* in some detail, she does not compare the teachings of Maa et al. with the claim limitations.

The claims require that the particles in the receptacle have a tap density of less than 0.4 g/cm^3 (limitation (i) of Claim 1). Maa *et al.* generically teaches that the tap density of their protein composition has a tap density of less than 0.4 g/cm^3, preferably less than 0.1 g/cm^3. Maa *et al.* does not teach in its working examples the actual tap density achieved by the process. However, without admission as to the accuracy of the assumption and for the purposes of responding to this office action, it will be assumed that at least some of the protein compositions produced by Maa *et al.* possess a tap density of less than 0.4 g/cm^3.

The claims require that at least about 50% of the particles have a fine particle fraction (FPF) less than 4.0 μm. See Claim 1, limitation (ii). As stated above, this limitation is not

addressed in the Summary or Detailed Description of Maa *et al.* There, Maa *et al.* defines "FPF" as being the percentage of the composition with "an aerodynamic mass median diameter of less than 6.8μm." (Col. 5, lines 60-62.)

The only discussion of other FPFs is limited to the Examples of Maa *et al.* Example 1 offers more data than Example 2 and measures the FPF of two protein compositions. As discussed above, the protein compositions are blended with a lactose carrier for the purpose of improving the FPF measurement. That is, the mass that resides within the inhaler does not consist of the protein composition. It consists of the protein composition and a lactose carrier. The lactose carrier is added to increase the FPF measurement. Thus, it can be inferred that the FPF of the protein composition in the absence of the carrier is less than the FPF measurement in the presence of the carrier.

Looking to Figure 5B of Maa *et al.*, the amount of protein composition deposited in Stage 4 and the Filter is less than 50%. In Figure 5A, the amount of protein composition deposited on Stage 4 was about 16%. The amount of protein composition deposited on the Filter was about 37%. Total amount of the protein composition with an FPF (<3 microns) was about 53%. As discussed above, since this measurement employed the use of a lactose carrier, it can be inferred that the measurement will be less without the lactose carrier.

Looking to Figure 6A of Maa *et al*, the device is not stated to measure the FPF of product but rather predicts the MMAD of the product. In any event, the cumulative % undersize of aerosolized powder below 4 microns is about 20%. Only after sonication, is the cumulative % undersize of fully dispersed raw spray dried (SD) powder below 4 microns about 50%. Clearly, the powder of Figure 6A would not possess an FPF under 4 microns of at least 50% either before or after sonication. Figures 6B and 6C report lower values at 4 microns than Figure 6A. The disclosed FPFs (<6.8 microns) in Table 3 appear to preclude an FPF (<4 microns) of greater than 50%.

What is clear is that Maa *et al.* teaches that these physical characteristics are not fixed values but change with the process used to produce the products. For example, the FPF of the rhDNase composition prepared by Maa *et al.* possessed an FPF (<6.8 microns) of 70% while the anti-IgE antibody compositions prepared by Maa *et al.* possessed an FPF (<6.8 microns) of 50%. Table 2 shows that changing a process parameter can impact the FPF value. Thus, it is clear

from Maa et al. that an FPF (< 4 microns) of at least 50% is not an inherent feature of the composition. As such, Maa *et al.* does not anticipate the limitation (ii) of Claim 1.

The claims require that at least about 50% of the particles be delivered to the patient. See Claim 1, limitation (iii). Like the previous limitation, this limitation is not addressed in Maa et al. Indeed, Maa *et al.* does not teach how much of the powders are actually delivered. The amount of a product that is delivered is, however, relates to the FPF. It is the amount of the respirable fraction of the product that exits the inhaler and deposits within the lung. See, for example, the discussion in Maa *et al.* in Col. 4. Further, delivery requires the product to remain in the lung and not be exhaled. J. Heyder, *et al., J. Aerosol Sci.*, 17:5 811-825 (1986). Thus, the delivered dose is expected to be lower than a reported FPF value. In this case, the only protein composition disclosed by Maa *et al.* that arguably possesses an FPF (<4 microns) of at least 40% is that depicted in Figure 5A. About 37% of the protein composition deposited on the filter and would therefore be exhaled, not deposited in the lung. As such, it would not be expected that the delivered dose of the composition would exceed 50%. As such, Maa *et al.* does not teach limitation (iii) of Claim 1, either explicitly or implicitly.

Finally, Claim 1, as amended, excludes the use of carriers to facilitate delivery of the particles. In each and every example, Maa et al. blend the protein composition with lactose carriers to facilitate delivery. Maa et al. teach that high FPFs (<6.8 microns, >40%) are achieved with homogenous blending with a carrier. Column 27, lines 44-45. As such, Maa et al. does not teach the use of a carrier-free product with high FPFs (<4 microns, >50%).

Anticipation requires that the reference teach each and every limitation of the claim. *Verdegaal Bros. v. Union Oil Co. of California,* 814 F.2d 628, 631 (Fed. Cir. 1987). As discussed above, the reference does not teach all of the limitations of the claims either explicitly or implicitly.

With regard to Claim 2, the claim requires the tap density of the particles to be less than 0.1 g/cm^3. The reference does not teach the tap density of the protein compositions made. At best, the reference provides only a generic disclosure of the limitation. It does not teach the combination of the claimed tap density, FPF (<4 microns), and delivery efficiency from a receptacle having a mass which consists of the particles. An anticipation rejection relying upon the picking and choosing amongst a plurality of variables in a generic disclosure can only be

found if the variables are sufficiently limited and well delineated. *Ex parte A*, 17 USPQ2d 1716 (BPAI 1990). Where, as here, the tap densities are not specifically disclosed at all in the exemplification and the exemplification is focused on other parameters (improving FPFs, dispersibility and protein stability, for example), it is difficult to imagine that selecting the recited tap density would be "at once envisaged" by the person of ordinary skill in the art, as contemplated in *In re Petering*, 301 F.2d 676 (CCPA 1962).

Claims 11 and 12 require the bioactive agent to be insulin and growth hormone. Example 1 prepared an antibody and rhDNase. Example 2 prepared rhIGF-1. It is clear from the examples that not all protein compositions possess identical properties. Thus, these proteins of Claims 11 and 12 are, at best, generically described. Maa et al. does not teach sufficient specifics to anticipate an insulin or growth hormone composition which possesses a tap density of less than 0.4 g/cm^3, an FPF (<4 microns) of at least 50% and a delivery efficiency of at least 50% from an inhaler in the absence of a carrier. Indeed, none of the working examples show that even the exemplified protein compositions possess the claimed limitations. Clearly, an insulin or growth hormone composition of the claims would not be "at once envisaged" by the person of ordinary skill in the art.

With regard to Claim 16, it is not at all clear that Maa *et al.* even generically disclose a hydrophobic drug. The Examiner is respectfully requested to point out support for her rejection of this claim.

With regard to Claim 17, the bioactive agent is a monoclonal antibody. The specific attempts by Maa et al. to make a highly dispersible monoclonal antibody failed to achieve a product that falls within the scope of the claim. For example, Example 1 teaches that the FPF (<6.8 microns) is 50%. The FPF (<3 microns) is only 20%. Obviously, the portion of the product that possesses an FPF (<4 microns) will be lower than 50%. Clearly, Maa *et al.* does not anticipate the claim.

Claim 21 requires the particles to be spray dried. Maa *et al.* teach away from spray drying, stating that spray freeze drying is a superior process. Since the claimed characteristics were not achieved by the spray freeze drying process taught by the reference, it is difficult to understand how Maa et al. anticipates a claim directed to a non-preferred embodiment.

Claim 20 is an independent claim and, like Claim 1, is not anticipated by Maa *et al.* and requires that at least about 5 milligrams (10 milligrams in the case of Claim 27) of agent be delivered in a single dose. As explained above, Maa *et al.* does not teach loading the inhaler with this amount of product. Examples 1 and 2 load only 1 to 2 milligrams of protein composition. Col. 17, lines 47-54. Clearly, less than all of the protein composition is delivered. Thus, the exemplification does not support the rejection. It is not seen where in the Summary or the Detailed Description even a generic disclosure of the product delivery in a single dose is taught. Clearly, the reference does not teach all of the limitations of Claim 20. Claim 24, which depends from Claim 20, presents a limitation discussed above in Claim 1; Claim 26, which depends from Claim 20, presents a limitation discussed above in Claim 21. As such, for the reasons set forth above, these claims are also not anticipated by the reference. Clearly, the combination of these limitations is not taught.

Withdrawal of the anticipation rejection is requested.

Rejection under 35 USC 103

Claims 1-27 are rejected as being anticipated by Maa *et al.* (US Patent No. 6,284,282 B1).

For all the reasons set forth above with respect to the anticipation rejection, the obviousness rejection of the claims also fails. In short, Maa *et al.* does not teach that the compositions of the present invention are possible. While it is true that Maa et al. teaches that the higher FPF the better, it does not teach that the FPFs, dosing efficiencies and amounts of dose as claimed in the present invention, in the absence of a carrier, are possible nor does it teach how one can make such compositions. The reference simply does not teach the present invention.

With respect to Claims 10, 13, 14 and 15, the claims are not directed to water-soluble proteins. Maa *et al.* is limited to proteins and the problems in formulating protein compositions for pulmonary delivery. One of ordinary skill in the art would not be motivated, with a reasonable expectation of success, to turn to Maa *et al.* to spray freeze dry a non-protein molecule, e.g. fluticasone. Certainly, the motivation to do so is not found in Maa *et al.*

With respect to Claims 23 and 25, the claim requires that at least 75% of the particles possess an FPF (<6.8 microns). It is noted that claims with this limitation have been previously held allowable by the Examiner. See the disposition of Claims 156 and 157 in the Examiner's Answer mailed April 21, 2004 in USSN 09/878,146 and the claims allowed in USSN 09/591,307. It is requested that the Examiner be consistent in this case. Indeed, Claims 23 and 25 are narrower in scope than the allowed claims and should be clearly allowable.

Provisional Rejection under Obviousness-type Double Patenting

Claims 1-27 have been provisionally rejected under the doctrine of obviousness-type double patenting over copending serial numbers 09/591,307 (allowed) and 09/878,146 (on appeal). While the undersigned disagrees with the Examiner's analysis that the present claims "fall entirely within the scope of the claims of [the copending applications]" and the inventions are the "same," it is agreed that there is an overlap in scope of claims. A terminal disclaimer is filed herewith to overcome the rejection based upon the allowed application. Upon resolution of the remaining issues in this or the appeal in the appealed application, a terminal disclaimer will be filed to overcome the second rejection.

CONCLUSION

In view of the above amendments and remarks, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

By

Carolyn S. Elmore
Registration No. 37,567
Telephone: (978) 251-3509
Facsimile: (978) 251-3973

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